Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

Supplement to ERG Report

Confidential: not for release

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No in confidence information included

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Supplement to Evidence Review Group report for consideration at the Appraisal Committee meeting (September 12, 2007)

Additional analyses concerning decision uncertainty

This supplement to the ERG report provides further information about aspects of decision uncertainty, which it is believed the Appraisal Committee may find helpful in there consideration of the cost-effectiveness of Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. The results shown below could not be generated in time to be included in the formal submission of the ERG report. However, in view of the potential complexity associated with comparing the relative merits of multiple treatment strategies, it was felt that the Committee may wish to refer to the additional table and charts shown below.

Net Benefit Estimates

Although cost-effectiveness comparisons are routinely made on the basis of the incremental cost-effectiveness ratio (ICERs), this measure alone does not indicate the likely magnitude of net benefit (health gains less additional costs) which can be expected. Table 1 shows calculations of net benefit for each of the three alternative rituximab treatment strategies compared to treatment without rituximab, alongside the corresponding ICERs. Since net benefit can be expressed in two ways (as a monetary amount per patient treated, or as a health outcome gain per patient) both figures are provided for convenience, although they are exactly equivalent. The calculation of net benefit is provided for two assumptions about the cash value of a QALY, corresponding to the two NICE threshold values (£20,000 and £30,000).

Comparing results for ‘induction only’ and ‘induction and maintenance’ in the submitted case, illustrates how similar ICER estimates may be associated with very different estimates of the magnitude of net benefit per patient. This may be important when considering whether an important difference exists between the likely effects of two strategies.

Table 1: Net Benefit of treatment strategies expressed in both monetary and utility units

Rituximab strategy	Incremental cost per patient	Incremental QALYs per patient	ICER	Net Benefit per patient			
				1 QALY ≡ £20,000		1 QALY ≡ £30,000	
				cash	QALYs	cash	QALYs
Submitted base case							
Induction only	£6,396	0.537	£11,916	+£4,340	+0.217	+£9,708	+0.324
Maintenance only	£5,731	0.632	£9,076	+£6,899	+0.345	+£13,214	+0.441
Induction & maintenance	£11,927	1.001	£11,910	+£8,101	+0.405	+£18,115	+0.604
ERG base case							
Induction only	£4,867	0.295	£16,488	+£1,037	+0.052	+£3,989	+0.133
Maintenance only	£3,497	0.267	£13,122	+£1,833	+0.092	+£4,498	+0.150
Induction & maintenance	£12,157	0.468	£25,978	-£2,797	-0.140	+£1,883	+0.063

Parameter Uncertainty

The ERG report noted that the absence of appropriate information on parameter uncertainty precluded the ERG from correctly re-estimating the Probabilistic Sensitivity Analysis contained in the manufacturer's submission. As a consequence the report could not comment with any confidence on the relative merits of the competing treatment strategies once the amendments identified in the model had been introduced.

However, it is possible to carry out an illustrative re-analysis based on a simple approximation, which is instructive in demonstrating how important the re-estimation of the effects uncertainty is to the decision in this appraisal. This involves calculating the average changes in incremental cost and incremental outcomes resulting from amendments to the deterministic model, and then using these to modify the detailed PSA results by these amounts. In effect this amounts to shifting the location of the PSA scatterplot in the cost-effectiveness plane, whist preserving all the relative position of the 2000 random iterations. This is not wholly reliable (since the ERG modifications will cause some more complex changes in relativities) and does not

replace the correct recalculation, but it is sufficient to indicate the sort of changes that could be expected to result and their consequences for decision-making.

In Figure S1 the cost-effectiveness acceptability curve (CEAC) is reproduced from the submitted model base case using the 4-arm model. This implies that only the 'maintenance only' or the 'induction and maintenance' strategies should be considered cost-effective and reliable (depending on the chosen threshold). By contrast Figure S2, based on the ERG amended model suggests that the two strategies for single use of rituximab appear to be similarly attractive, and both seem to out-perform the dual-use strategy throughout the normal threshold range.

This raises the possibility of recommending that either of the single use strategies could be adopted (i.e. based on local policy or clinician preference) if the differences between their effects (net benefit) and reliability (probability cost-effective) were not deemed to warrant preferring one over the other. In this case, it would be appropriate to re-estimate the CEAC, for each single-use strategy separately excluding the other single-use option. The results are shown in Figures 3 and 4, and indicate that either option leads to probability estimates in the range 60-75% when the threshold is between £20,000 and £30,000 per QALY gained.

It is important to restate that the PSA on the ERG amended model should be carried out properly without approximations, using accurate trial-based measures of parameter uncertainty, since the results can be very sensitive to small changes in inputs and assumptions.

Figure S1: Submitted model base case 4-arm cost-acceptability plot

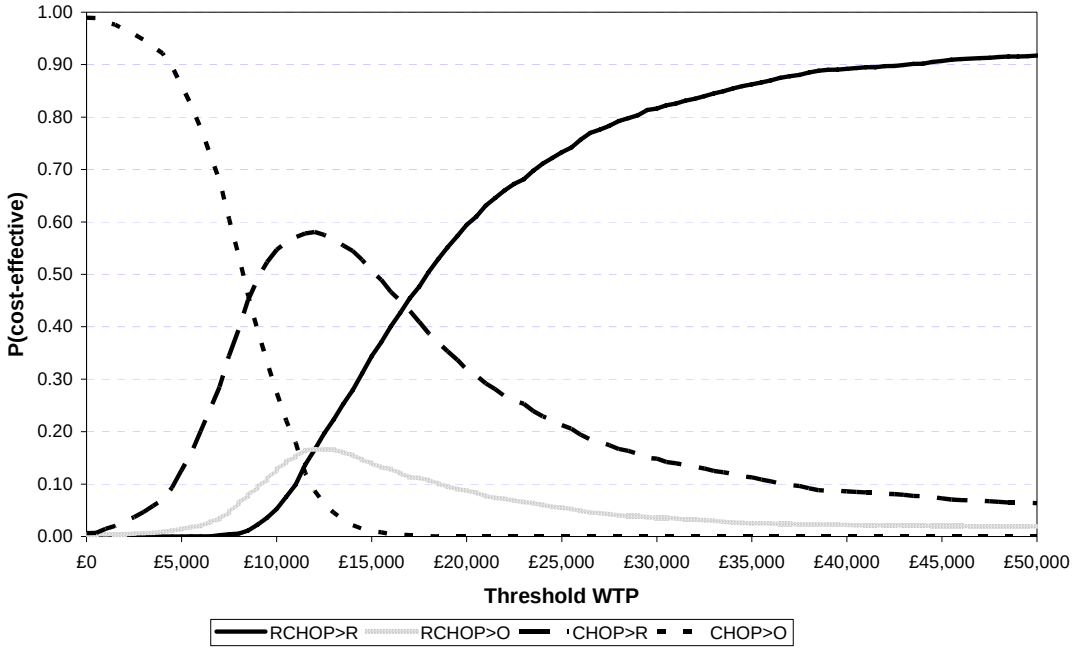

Figure S2: ERG amended model base case 4-arm illustrative cost-acceptability plot

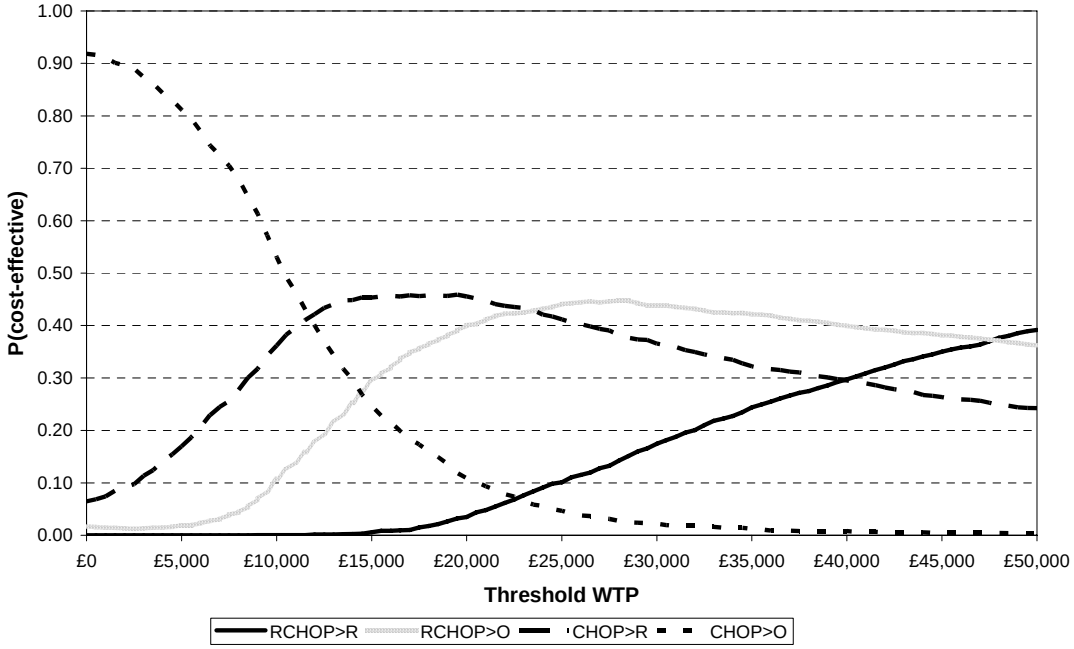

Figure S3: ERG amended model base case 4-arm illustrative cost-acceptability plot - excluding the maintenance-only rituximab option

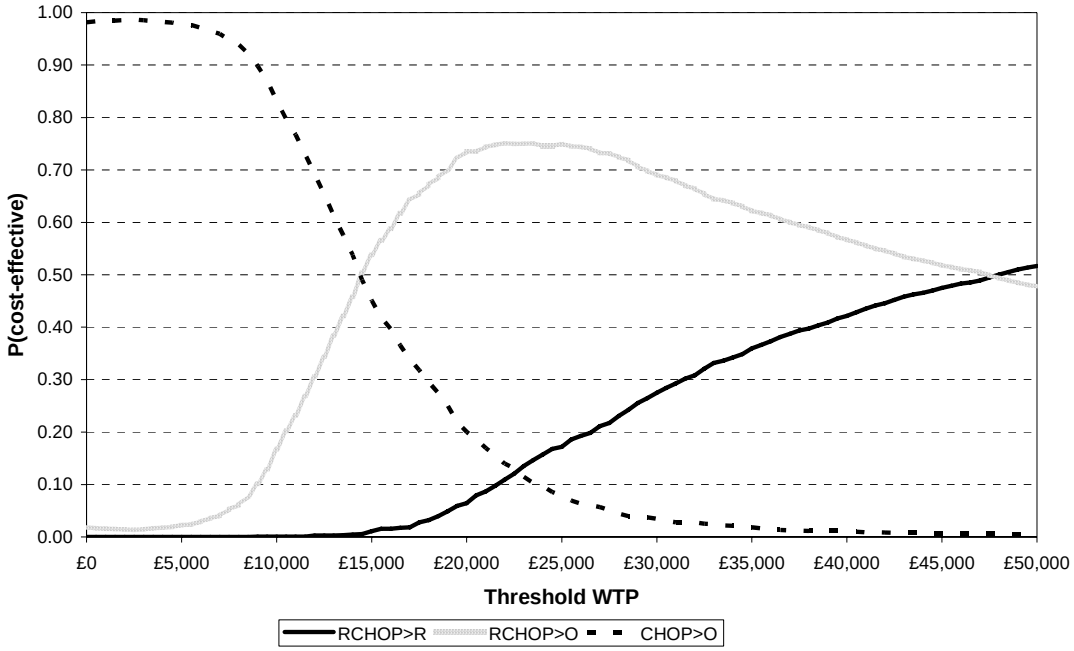

Figure S4: ERG amended model base case 4-arm illustrative cost-acceptability plot - excluding the induction-only rituximab option